S.M.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/921,157	08/02/2001	Antonello Covacci	CHIR-0315	7773

7590 03/03/2004

REBECCA N, HALE, ESQ
CORPAORTATE PATENT COUNSEL CHIRON CORP
INTELLECTUAL PROPERTY-R440,
P.O. BOX 8097
EVERYVILLE, CA 94608-2917

EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 03/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/921,157	COVACCI ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38 and 44-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38 and 44-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Request for Continued Examination

1) A request for continued examination under 37 C.F.R 1.114, including the fee set forth in 37 C.F.R 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R 1.114, and the fee set forth in 37 C.F.R 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R 1.114. Applicants' submission filed on 11/26/03 has been entered.

Applicants' Amendment

2) Acknowledgment is made of Applicants' amendment filed 11/26/03 in response to the final Office Action mailed 06/04/03. With this, Applicants allege that the finality of the Office Action mailed 06/04/03 is improper under 35 U.S.C. § 132, because the new ground rejection was not necessitated by Applicants' amendment, or because the new rejection based on newly cited art in response to an amendment 'should reasonably have been expected' by the Office. Applicants allege that 'the 35 U.S.C § 102(e) rejection for alleged obviousness of claims 44 and 46' is a new ground of rejection, not necessitated by Applicants' amendment.

The Office disagrees. First, no 'obviousness' rejection was made to reject claims 44 and 46 in the Office Action that was made final. Secondly, claim 44, as amended by Applicants, and the new claim 46, both presented via the amendment filed 03/17/03, are reproduced herebelow [Emphasis in original]:

> 44. (amended) (A prophylactic or therapeutic vaccine) An immunogenic composition comprising an immunologically effective amount of a recombinantly produced *H. pylori* (CT) cytotoxin polypeptide comprising a fragment of an amino acid sequence of SEQ ID NO: 3, wherein said recombinantly produced polypeptide (i) (can induce the production of antibodies to) is immunologically identifiable by an antibody that reacts specifically with *H. pylori* cytotoxin and (ii) exhibits substantially no toxicity, or substantially reduced contribution to toxicity, and a pharmaceutically acceptable carrier.
>
> 46. (New) An immunogenic composition comprising an immunologically effective amount of a recombinantly produced *H pylori* cytotoxin polypeptide comprising a fragment of an amino acid sequence of SEQ ID N0: 3, wherein said recombinantly produced polypeptide (i) is immunologically identifiable by an antibody that reacts specifically with *H. pylori* cytotoxin and (ii) exhibits substantially no toxicity, or substantially reduced contribution to toxicity.

Neither the changes introduced to claim 44, nor the new claim 46 presented by Applicants via the amendment filed 03/17/03, were suggested by the Office. The Office could not have reasonably expected the amendments introduced to claim 44 or the submission of the new claim 46. On the other hand, in the face of the rejections made under 35 U.S.C. § 112, first paragraph, both due to inadequate written description and the lack of enablement via the Office Action mailed 10/15/02, especially with regard to the limitation 'fragment .....' in claims 39 and 40, the Office reasonably expected Applicants **not** to introduce the limitation via an amendment to the existing claim 44, or via the new claim 46. The newly added limitation, such as, 'fragment' and 'immunologically identifiable ..... cytotoxin' necessitated the new rejections.

Therefore, the finality of the Office Action mailed 06/04/03 was proper.

Status of Claims

3) Claims 41-43 have been canceled via the amendment filed 11/26/03.

Claims 38 and 44-46 have been amended via the amendment filed 11/26/03.

Claims 38 and 44-46 are pending and are under examination.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Rejection(s) Maintained

6) The provisional rejection of claims 38 and 44 made in paragraph 9 of the Office Action mailed 10/15/02 (paper no. 12) under the judicially created doctrine of obviousness-type double patenting over the cited claims of the co-pending application, 09/360,934, is maintained for reasons set forth therein. It is noted that Applicants have agreed to submit a terminal disclaimer over SN 09/360,934 upon indication of allowability of the claims.

7) The rejection of claims 38 and 44-46 made or maintained in paragraph 10(d) of the Office Action mailed 10/15/02 (paper no. 12) and paragraph 20 of the Office Action mailed 06/04/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is maintained for reasons set forth therein and herebelow.

Applicants point to MPEP 2173.05 (b) and contend that the term 'substantially' often is used in conjunction with another term to describe a particular characteristic of a claimed invention. Applicants cite case law and state that definiteness will be found for use of the term 'substantially' where there are general guidelines in the specification, or where one of ordinary skill in the art would understand the meaning of the term. Applicants assert that both of these instances occur in the present case. Applicants point to the previous Del Giudice declaration and restate that one of ordinary skill in the art would understand the use of the term 'substantially' in the recited phrase to mean that the polypeptide or fragment being described does not exhibit statistically significant cytotoxic effects. Applicants further state the following:

> Moreover, the specification provides very clear guidance as to the meaning of the term "substantially" as used in the specification. For example, at page 16, lines 19-29, the term "purified" and "isolated" are defined as "substantial absence of other biological macromolecules of the same type" – i.e., "at least 75% by weight, more preferably at least 85% by weight, more preferably still at least 95% by weight, and most preferably at least 98% by weight, of biological macromolecules of the same type". In other words, substantially pure means at least 75% pure. *Similarly*, "substantially no toxicity or a substantially reduced

toxicity" means at least a 75% reduction in toxicity. [Emphasis added].

Applicants further state that the terms 'toxin' and 'cytotoxin' and 'derivatives thereof' are used interchangeably in the specification. Applicants point to page 5, line 31 to page 6, line 11 and state that 'cytotoxin' and 'toxin' are defined synonymously in the specification. Applicants contend that the 140 kDa protein set forth in Figure 2 is the precursor protein to the 100 kDa polypeptide having cytotoxic (i.e., vacuolating) activity.

Applicants' arguments have been carefully considered, but are non-persuasive. The Del Giudice declaration has been fully addressed by the Office previously. The term 'substantially' in the instant claims is not associated with 'purity', but with 'toxicity', including the intrinsic toxicity. A description provided for the term 'purified' and 'isolated' cannot and does not constitute the definition for the term 'substantially no toxicity' or 'a substantially reduced toxicity'. It is important to note that the polypeptide in the currently claimed composition is neither an 'isolated' nor a 'purified' polypeptide. *Arguendo*, even if one equates the description for the terms 'isolated' and 'purified' with the term 'substantially no toxicity' or 'a substantially reduced toxicity', it is unclear how a substantial absence of other biological macromolecules 'of the same type' by at least 75% by weight can render the instantly claimed product a product of 'substantially no toxicity' or a product of 'substantially reduced toxicity'. As set forth previously, the term 'toxicity' encompasses cytotoxicity, endotoxicity, exotoxicity, cell-vacuolizing toxicity, or any other type of general or specific toxicity. The paragraph bridging pages 5 and 6 of the specification describes a 'cytotoxin' or 'toxin' of *H. pylori* which causes 'vacuolation and death of a number of eukaryotic cell types', but not a recombinant cytotoxin of SEQ ID NO: 3 or a fragment thereof of the recited length which is of 'substantially no toxicity' or of 'substantially reduced toxicity'. It is unclear how a cytotoxin that causes the death of a number of eukaryotic cells can be viewed as being equivalent to a recombinant cytotoxin having a substantial absence of other biological macromolecules 'of the same type' by at least 75% by weight. The only place where the phrases were mentioned in the specification as originally filed was in some original claims. Thus, contrary to Applicants' assertion, there appears to be no general guidelines or definition for these phrases in the specification for one to understand the meaning or scope of the phrases, or the difference between the two phrases.

8) The rejection of claims 38 and 44-46 made or maintained in paragraph 12 of the Office Action mailed 10/15/02 (paper no. 12) and paragraph 21 of the Office Action mailed 06/04/03 under 35 U.S.C. § 112, first paragraph, as being non-enabled, is maintained for reasons set forth therein and herebelow.

Applicants cite MPEP § 2164.01 and case law, and contend that the test is whether the disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention without undue experimentation. Applicants

acknowledge that the *H. pylori* cytotoxin described at page 5, lines 35-39 and page 46, lines 7-29, 'causes formation of vacuoles in eukaryotic cells'. Applicants submit that the claimed polypeptide, for example, 'may be' a genetically or chemically detoxified form of the cytotoxin, or a fragment of the native cytotoxin, having no toxicity. Applicants state that the polypeptide, however, exhibits substantially no toxicity, or substantially reduced toxicity by virtue of being recombinantly produced. Applicants then cite the post-filing publication of Manetti *et al.* (*Infect. Immun.* 63: 4476-4480, 1995) and state that the recombinantly produced '95 kDa polypeptide' taught by Manetti *et al.* indeed lacks toxicity, while being immunogenic. Applicants further cite yet another post-filing reference of Ghiara *et al.* (*Infect. Immun.* 65: 4996-5002, 1997), but provide no explanation as to its relevance to the instant rejection. Applicants cite case law and state that it is axiomatic that the patent applicant need not teach 'which is known in the art'. Applicants mention about the Del Giudice Declaration, which allegedly stated that methods of chemical and genetic inactivation of toxins were known to those of skill in the art in March 1992 and that it would have been routine to determine cytotoxin fragments that exhibit substantially no toxicity or substantially reduced toxicity. Applicants state that toxicity could be measured in *in vitro* vacuolation assays and in animal models of *H. pylori* infection. Applicants point to page 15, lines 14-17; and page 38, line 31 to page 41, line 17 of the specification, and contend that the specification contemplates immunogenic compositions comprising cytotoxin polypeptides that are capable of eliciting protection against *H. pylori*. Applicants submit that the specification at page 15, lines 18-21 states that the '*H. pylori* proteins ... may be used for producing antibodies, either monoclonal or polyclonal, *specific to* the proteins' [Emphasis in original]. Applicants further point to the specification at page 45, line 25 to page 46, line 6 as describing a fusion protein comprising the amino acids encoded by nucleotides 116-413 of the nucleotide sequence SEQ ID NO: 2 which generated rabbit antibodies that recognized the 100 kDa *H. pylori* protein associated with vacuolation' – i.e., was immunologically identifiable by rabbit antibodies that recognize the toxic form of *H. pylori* cytotoxin. Applicants conclude that that the methods used to produce a polypeptide exhibiting substantially no toxicity or substantially reduced toxicity may reduce the effective immunogenicity relative to the fully toxic polypeptide is irrelevant to the enablement analysis so long as some level of immunogenicity remains.

Applicants' arguments have been carefully considered, but are non-persuasive. It is noted that what is claimed in the instant claims is a *H. pylori* (cytotoxin) polypeptide, recombinant or otherwise, which "exhibits substantially no toxicity" or "substantially reduced toxicity". Contrary to Applicants' assertion, the disclosure, when it was filed, did not contain sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention without undue experimentation. The term 'genetic detoxification' or 'chemical detoxification' does not appear within the instant specification, as originally filed. The instant specification does provide sufficient functional and

structural characteristics of a fully cytotoxic polypeptide of *H. pylori* that has the amino acid sequence of SEQ ID NO: 3. The paragraph bridging pages 5 and 6 of the specification describes the molecular weight and the ability of such a *H. pylori* cytotoxin to cause 'vacuolation and death of a number of eukaryotic cell types'. The ability to cause vacuolation and death positively represents the ability of the polypeptide to be 'toxic' or 'cytotoxic', as opposed to its ability to be substantially non-cytotoxic or less cytotoxic. The paragraph bridging pages 45 and 46 describes the immunological reactivity of protein extracts from 'cytotoxin positive' strains of *H. pylori*. See paragraph 9 below for a detailed rebuttal with regard to what is and what is not disclosed in this part of the specification. There are no non-cytotoxic or less cytotoxic recombinant polypeptides of SEQ ID NO: 3, or five-mer, ten-mer, or fifteen-mer fragments thereof described therein, which at the same time show the specific immunological reactivity as recited. Furthermore, there is no showing that a chemically detoxified form of the cytotoxin, a fragment of the 'native' cytotoxin, or a genetically 'detoxified' form of the cytotoxin, a five-mer, a ten-mer or a fifteen-mer thereof, has the recited immunological function(s) or specificity. Applicants did not have possession of a genetically detoxified form of the cytotoxin of *H. pylori* having the full structure of SEQ ID NO: 3or a five-mer, ten-mer or a fifteen-mer thereof, that had the recited immunological property or specificity. Applicants have not even shown that 'some level of immunogenicity' remains in the 'genetically detoxified' *H. pylori* cytotoxin that exhibits substantially no cytotoxicity or substantially reduced cytotoxicity. What is important is whether or not the substantially non-toxic or less toxic genetically detoxified five-mer, ten-mer or fifteen-mer or longer *H. pylori* cytotoxin polypeptide retains the immunogenicity that is relevant to the purpose of the instant invention in that the antibodies produced by such substantially non-toxic or less toxic or genetically detoxified *H. pylori* cytotoxin recognize the native cytotoxic polypeptide. *H. pylori* cytotoxin polypeptides, with or without the alleged ability to elicit protection against *H. pylori,* and whether or not native *H. pylori* proteins may be used for producing antibodies, either monoclonal or polyclonal, specific to themselves are not the issues. See the claim language. Contrary to Applicants' assertion, at the time of the instant invention, it was **not** known in the art how to produce a detoxified recombinant *H. pylori* cytotoxin of SEQ ID NO: 3, or an at least 5-mer, 10-mer, or fifteen-mer detoxified fragment thereof, such that it retained the ability to be immunologically identifiable by antibodies reactive specifically with the polypeptide of the amino acid sequence, SEQ ID NO: 3. Therefore, those of skill in the art could not have envisioned the structure of the claimed polypeptide commensurate in scope with the recited functions. With regard to Applicants' citation of Manetti *et al.*, Manetti's 1995 post-filing disclosure of a 95 kDa *H. pylori* cytotoxin does not and cannot provide enablement for the recombinant cytotoxin of *H. pylori* of the instant invention, or fragments thereof having the function(s) or characteristics as claimed. The courts have held that it is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute

adequate enablement. See *Genentech Inc., v. Novo Nordisk A/S Ltd., 42 USPQd 1001*. Moreover, the specification must have been enabling at the time the invention was made and developments after the time of filing are of no consequence to what one skilled in the art would have believed at the time of filing (*In re Wright, 27 USPQ2d 1510*). A review of the second post-filing 1997 reference mentioned by Applicants, Ghiara *et al.* (*Infect. Immun.* 65: 4996-5002, 1997), indicates that this reference has nothing to do with the claimed cytotoxin of SEQ ID NO: 3.

The genetic detoxification alluded to in the Del Giudice Declaration was not contemplated in the instant specification, as originally filed. Nowhere in the specification can one find the direction and guidance to produce detoxified cytotoxins of *Helicobacter pylori,* or their fragments of the recited length, such that they possess substantial non-cytotoxicity, or substantially reduced cytotoxicity and at the same time remain immunologically identifiable by an antibody that reacts specifically with *Helicobacter pylori* cytotoxin of SEQ ID NO: 3. The Del Giudice Declaration discusses pertussis toxin, which has a structure distinct from the instantly claimed product. Further, the Declaration does not address the 'unpredictability' factor. The teaching in the specification is contrary to what Applicants state. For example, at page 7, lines 33-37, the specification teaches polypeptide molecules having amino acid substitutions 'that do not substantially affect the functional aspects', i.e., cytotoxin polypeptides having amino acid substitutions such that their cytotoxic activity remains substantially the same as the native polypeptide. Therefore, using the application as a guide, one of ordinary skill in the art would have been able to produce *Helicobacter pylori* cytotoxin polypeptides that retain substantial cytotoxicity. The specification, for example, in the second paragraph on page 7, mentions of conservative amino acid replacement and states that 'it is reasonably predictable that an isolated replacement of a leucine with isoleucine ... or a similar conservative replacement of an amino acid with a structurally related amino acid will not have a major effect on the biological activity'. The biological activity includes cytotoxicity. There is no disclosure as to which amino acids at which positions can be substituted such that one can obtain the recombinant polypeptide, or a five-mer, ten-mer, or a fifteen-mer fragment thereof that has the recited immunological specificity along with substantial non-toxicity. Therefore, it is reasonable to conclude that the retention of immunologic identifiability concurrently with the substantial attenuation of cytotoxicity of a cytotoxin has not been demonstrated and is not predictable without a clear showing, and would have required a considerable amount of undue experimentation. The specification recites therapeutic, prophylactic and diagnostic applications or vaccine intentions for the claimed polypeptide products. However, the instant specification fails to teach such non-cytotoxic polypeptides, which concurrently have the ability to bind to a SEQ ID NO. 3-specific antibody. The Manetti's post-filing publication in fact provides the *prima facie* evidence that in 1995, about three years after the effective filing date of the instant invention, there was no predictability in obtaining the claimed

detoxified *Helicobacter pylori* cytotoxin polypeptide fragments that are conformationally competent and therefore immunolgically functional. In 1995, Mannetti *et al.* taught the conformational complexity of a *Helicobacter pylori* cytotoxin polypeptide. Manetti *et al.* also taught that the immune response is primarily due to conformational epitopes. Manetti *et al.* specifically taught that "[e]ven partial destruction of the conformational epitopes by chemical inactivation can result in lowering of the effective immunogenicity". With regard to the genetic detoxification, Manetti *et al.*, in 1995, stated that a "genetically detoxified molecule which retains the native structure **will be** an important goal" (see page 4479), thus indicating that genetic detoxification of *Helicobacter pylori* cytotoxin was not achieved at least until 1995. Manetti's reference in fact supports the Office's position by establishing that, in 1995, a *Helicobacter pylori* cytotoxin produced recombinantly 'lacked any biological activity' and 'failed to induce neutralizing antibodies after immunization of rabbits' (see abstract of Manetti *et al.*). A recombinant cytotoxin that induces non-neutralizing antibodies would not be expected by those of skill in the art to be of any prophylactic or therapeutic value, and such a product would defeat the purpose of the instant invention. Pizza's disclosure on pertussis toxin alluded to in the Del Giudice Declaration cannot and does not provide enablement for the structurally unrelated *Helicobacter pylori* cytotoxin polypeptide. Although one may be able to produce fragments of SEQ ID NO: 3 and test their cytotoxicity and immunological identifiability, given the art-disclosed conformational complexity and functional unpredictability, the maintenance of immunological identifiability by an antibody specifically reactive with the native cytotoxin polypeptide of SEQ ID NO: 3 along with the concurrent acquisition of the recited attenuation in cytotoxic activity following one or more amino acid substitutions in the cytotoxin polypeptide, would not have been predictable, absent a detailed guidance or a concrete showing. Certainly, retention of conformational epitopes within a five-mer, ten-mer or fifteen-mer fragment of a recombinant polypeptide of SEQ ID NO: 3 such that it is immunologically reactive with an antibody specific to the native polypeptide and at the same time non-cytotoxic or substantially less cytotoxic is not a predictable event. Regardless of the complexity or simplicity of the method of isolation and method of testing, conception cannot be achieved until reduction to practice has occurred. In light of the unpredictability disclosed in the art and the Manetti teachings published in 1995, it does not appear that Applicants were in possession of the claimed product, wherein the product is required to possess the two specific functions recited in the claims. It should be noted that the only place where the phrase 'substantially no toxicity' or 'substantially reduced toxicity' was mentioned in the specification as originally filed was in some original claims. Other than this, there is no direction and guidance as to how to produce either a full length cytotoxin of SEQ ID NO: 3 or fragments thereof, including recombinant ones, which possess the two required functions: i) substantially no cytotoxicity, or substantially reduced cytotoxicity, and ii) immunological identifiability by an antibody that reacts specifically with *Helicobacter*

pylori cytotoxin of SEQ ID NO: 3. The definition for 'cytotoxin' provided in the instant specification is a non-limiting definition for a polypeptide, which does not exclude a processed 100 kDa polypeptide possessing cytotoxic activity. Applicants' remarks about the specification at page 45, line 25 to page 46, line 6 have been addressed below. See paragraph 9 below. Clearly, the evidence submitted is insufficient to establish a conception of the invention prior to the effective date of the invention. While conception is the mental part of the inventive act, it must be capable of proof, such as by demonstrative evidence or by a complete disclosure to another. Conception is more than a vague idea of how to solve a problem. The requisite means themselves and their interaction must also be comprehended. See *Mergenthaler v. Scudder*, 1897 C.D. 724, 81 O.G. 1417 (D.C. Cir. 1897). The rejection stands.

It is further emphasized that predictability or unpredictability is one of the *Wands* factors for enablement. The following analysis is made to document that, at the time of the invention or even a couple of years after the effective filing date of the instant application, one could not have obtained, with predictability, *H. pylori* cytotoxin polypeptide or five-mer, ten-mer or fifteen-mer fragments having substantially no cytotoxicity or substantially less cytotoxicity, which at the same time have the recited immunological specificity. With regard to Applicants' remarks on genetic detoxification, it should be noted that the art of bacterial toxins indicates that even a single amino acid substitution in a polypeptide will often dramatically affect the biological activity and characteristics of a protein or a polypeptide. The publication of Pizza *et al.* (*Mol. Microbiol.* 14: 51-60, 1994) and the patent of Clements *et al.* (US 6,019,982) establish how one of skill in the art would have been forced into undue experimentation to obtain the claimed product. For instance, in 1994, Pizza *et al.* showed that replacement of amino acids at random positions in *E. coli* LT-A polypeptide, for example, His-70, Val-60, Ala-45 and Leu-4, resulted in the "collapse of the protein structures" and altered "the structural assembly" (see page 54, last two lines, and page 57) of the proteins. The art has further established that substitution of any amino acid at any given position of the A subunit of the LT toxin polypeptide did not always result in a functional or desired mutant toxin. For instance, while replacement of Val at position 53 of LT with Glu or Asp resulted in a non-toxic functional mutant LT, the substitution with Tyr at the same position caused the collapse and prevention of the structural assembly of the A subunit. Thus, there is no certainty that amino acid substitutions at any position would yield a bacterial polypeptide that retains the function of the native polypeptide. The art reflects that while the substitution of Arg at position 192 of LT with Gly resulted in a less toxic adjuvantic mutant LT (see Clements *et al.*, US 6,019,982), the substitution of Arg at the same position 192 with Asn did **not** reduce the toxicity of LT (see abstract; page 57; and Table 1 of Pizza *et al.*, 1994). Similarly, it has been shown in the art that attenuation of the hemolytic activity of a wild-type pneumolysin by any random mutation is unpredictable. For instance, Feldman *et al.* (*Am. J. Respir. Cell Mol. Biol.* 5: 416-423, 1991) showed that a Tyr 384 > Phe modification

results in a modified pneumolysin that had normal hemolytic (toxic) activity (see page 417). The state of the art clearly suggests that a mutation at any random position does not result in a modified pneumolysin polypeptide with an attenuated hemolytic activity. Mitchell *et al.* (*Mol. Microbiol.* 5: 1883-1888, 1991) showed that individual modifications of Trp 379 and Trp 397 to Phe, or of residues Tyr 384 and Asp 385 to Phe and Asn respectively, did not alter the cytolytic activities of resultant modified pneumolysins (see page 1885, left column). The state of the art in 1998 showed that an Asp 385 >Asn mutation in the pneumolysin gene resulted in a modified pneumolysin that retained 100% hemolytic (toxic) activity of the wild-type pneumolysin (see Table 1 of Alexander *et al. Microb. Pathogen.* 24: 167-174, March 1998). Thus, it appears that there was considerable unpredictability in the art at the time of the invention as to which of the amino acid substitution(s) at any specific position(s) would preserve the structural and functional integrity of a bacterial polypeptide and render the polypeptide still suitable for use in a vaccine or diagnostic composition. Thus, both the pre-filing and the post-filing disclosures support the position taken by the Office with regard to the lack of enablement of the instant claims.

9) The rejection of claims 38 and 44-46 made in paragraph 22 of the Office Action mailed 06/04/03 under 35 U.S.C. § 112, first paragraph, as containing new subject matter, is maintained for reasons set forth therein and herebelow.

Applicants contend that support for the limitations 'immunologically identifiable by antibodies, which react specifically with the polypeptide having the amino acid sequence of SEQ ID N: 3' is found throughout the specification as filed. Applicants point to claim 8 as originally filed, lines 18-20 of page 15 and page 45, line 26 to page 46, line 6 and state that the specification discloses the preparation of antisera against the *Helicobacter pylori* cytotoxin and the use of the antisera to specifically detect polypeptides immunologically identifiable with the *H. pylori* cytotoxin.

Applicants' arguments have been carefully considered, but are non-persuasive. What is claimed in the instant claims is a polypeptide, recombinant or otherwise of any length, starting from a five-mer, a ten-mer, a fifteen-mer etc., from the amino acid sequence of SEQ ID NO: 3, which while exhibiting substantially no toxicity or substantially reduced toxicity, is also 'immunologically identifiable by antibodies that react specifically with the polypeptide having the amino acid sequence of SEQ ID NO: 3'. The parts of the specification pointed to by Applicants do not support such a five-mer, ten-mer, fifteen-mer etc. or a polypeptide of SEQ ID NO: 3 being immunologically identified by 'antibodies that react specifically with the polypeptide having the amino acid sequence of SEQ ID NO: 3' which polypeptide exhibits substantially no toxicity or substantially reduced toxicity. On the other hand, the specific parts of the specification describe rabbit antisera containing antibodies raised using a partially purified fusion protein that comprises the amino acids of the 'cytotoxin' polypeptide encoded by nucleotides 116-413 of the nucleotide sequence shown in

Figure 1 (SEQ ID NO: 2). There is no descriptive support that this particular fragment in the fusion protein exhibits substantially no toxicity of any kind including cytotoxicity, or exhibits substantially reduced toxicity of any kind, including cytotoxicity. The antisera thus produced using a specific fragment of SEQ ID NO: 3 encoded by nucleotides 116-413 of the nucleotide sequence shown in Figure 1 (SEQ ID NO: 2) is used to 'probe protein extracts from a cytotoxin positive and a cytotoxin negative strain' of *H. pylori* by immunoblotting. The antisera detected a polypeptide in the protein extracts of the 'cytotoxin positive' strain, the amino acid sequence of which polypeptide is unknown. The polypeptide identified by the antisera is a polypeptide present in the protein extracts of a cytotoxin-producing strain of *H. pylori,* whose amino acid sequence is not described as being SEQ ID NO: 3. A polypeptide present in the protein extracts of a cytotoxin-producing strain of *H. pylori* is expected to be fully cytotoxic, as opposed to be substantially non-cytotoxic. Therefore, the description in pages 45 and 46 does not and cannot provide support for a polypeptide that is a five-mer, ten-mer, fifteen-mer etc. from SEQ ID NO: 3, or even a full length polypeptide that exhibits substantially no toxicity, or substantially reduced toxicity and which is also immunologically identifiable by antibodies that react specifically with the polypeptide having the amino acid sequence of SEQ ID NO: 3. There is no descriptive support for a single non-toxic or non-cytotoxic five-mer, decamer, fifteen-mer, twenty-mer polypeptide etc. from SEQ ID NO: 3 that is also immunologically identifiable by antibodies that react specifically with the polypeptide having the amino acid sequence of SEQ ID NO: 3. The rejection stands.

10) The rejection of claims 44 and 46 made in paragraph 24 of the Office Action mailed 06/04/03 under 35 U.S.C. § 102(e) as being anticipated by Cover *et al.* (US 6,054,132, filed 02/26/1992), is maintained for reasons set forth therein and herebelow. See the following paragraph.

Claims 38 and 45 are now included in this rejection.

11) The rejection of claims 44 and 46 made in paragraph 25 of the Office Action mailed 06/04/03 under 35 U.S.C. § 102(b) (not 102e) as being anticipated by Cover *et al.* (*J. Biol. Chem.* 267: 10570-10575, 25 May 1992 - Applicants' IDS) (Cover *et al.*, 1992), is maintained for reasons set forth therein and herebelow. See the following paragraph.

Claims 38 and 45 are now included in this rejection.

Applicants preliminarily and correctly note that Cover *et al.* (*J. Biol. Chem.* 267: 10570-10575, 25 May 1992) is not prior art under 35 U.S.C. § 102(e).

Applicants cite case law and state that to anticipate a claim, a prior art reference must teach, either expressly or inherently, each and every element of the claim. Applicants contend that the '132 patent discloses the purification from *H. pylori* culture supernatant of a vacuolating toxin having a molecular weight of 87 kDa. Applicants point to Table 1 of the '132 patent and state that the prior art purification scheme

resulted in a greater than 5000-fold increase in specific activity of the toxin measured as a function of cell vacuolating activity. Applicants make a similar remark with regard to the teachings of Cover *et al.* (*J. Biol. Chem.* 267: 10570-10575, 25 May 1992). With this, Applicants conclude that the '132 patent does not teach a polypeptide of the present claims possessing substantially no toxicity or substantially reduced contribution to toxicity.

Applicants' arguments have been carefully considered, but are non-persuasive. The typing of '102(e)' as opposed to '102(b)' in paragraph 25 of the Office Action mailed 06/04/03 was due to an inadvertent typographical error, which has been corrected hereby.

As set forth previously, Cover *et al.* ('132) disclosed an antigenic polypeptide of a cell vacuolating toxin (i.e., cytotoxin) of *Helicobacter pylori* which is recombinantly or synthetically produced, and a composition comprising the same (see column 2, lines 25-58). The polypeptide comprises a 23 amino acid-long N terminus of the toxin antigen, i.e., SEQ ID NO: 1, and is obtained from the purified polypeptide (see column 10, lines 2-4; and first sequence in columns 17 and 18 under Sequence Listing). The 23 amino acid-long antigenic portion of the polypeptide of the prior art, AFFTTVIIPAIVGGIATGTAVGT, has 100% sequence or structural identity with a 23 amino acid-long contiguous portion that stretches between positions 34-56 of the instantly recited SEQ ID NO: 3. The antigenic polypeptide is present along with water, phosphate buffered saline or an adjuvant (see column 18, third paragraph; column 17, second paragraph; and column 16, lines 45-50). The polypeptide has a molecular weight of 87,000 or 972,000 daltons (see column 2, seventh full paragraph). That the structurally identical 23 amino acid-long antigenic polypeptide of the prior art obtained from a purified toxin, is pure enough to be of substantially no endotoxicity, or of substantially reduced LPS-related toxicity, and is long enough to be immunologically identifiable by antibodies specific to the amino acid sequence of SEQ ID NO: 3 are inherent from the teachings of Cover *et al.* ('132). Given that the structural elements of the instant claims are met by the prior art antigenic polypeptide, the immunological identifiability by antibodies specifically reactive with the amino acid sequence of SEQ ID NO: 3 and/or the exhibition of substantially no toxicity or of substantially reduced toxicity, including cytotoxicity, are viewed as the inherent properties inseparable from the antigenic polypeptide taught by Cover *et al.* ('132).

Similarly, Cover *et al.* (1992) disclosed a polypeptide comprising an antigenic N-terminal portion of a cell vacuolating toxin (i.e., cytotoxin) of *Helicobacter pylori,* which is recombinantly or synthetically produced and a composition comprising the same in distilled water (see Table III and page 10571, left column). This polypeptide comprising the 23 amino acid-long portion is obtained from the purified toxin antigen and has 100% sequence identity with a 23 amino acid-long contiguous polypeptide portion that stretches between positions 34-56 of the instantly recited SEQ ID NO: 3, AFFTTVIIPAIVGGIATGTAVGT

(Table III). The polypeptide has a molecular weight of 87,000, or 972,000 daltons (see page 10573, right column; and page 10574, left column). That the polypeptide comprising the 23 amino acid-long antigenic portion of the prior art, obtained from a purified toxin, is pure enough to be of substantially no endotoxicity, or exhibits substantially reduced contribution to LPS-related toxicity, and is long enough to be immunologically identifiable by an *H. pylori*-specific antibody are inherent from the teachings of Cover *et al.* Given that all the structural elements of the instant claims are met by the prior art antigenic polypeptide, the immunological identifiability by an antibody specifically reactive with *H. pylori* cytotoxin and the exhibition of substantially no toxicity, or of substantially reduced toxicity, including cytotoxicity, are viewed as the inherent or intrinsic properties inseparable from the antigenic polypeptide taught by Cover *et al.* (1992).

The prior art polypeptide is structurally identical to the instantly claimed polypeptide, irrespective of how it is obtained. Furthermore, the term "recombinant" and/or "expressed from ..... nucleotides of SEQ ID NO: 2" in some of the claims represent process limitations. When claims are drawn to a product-by-process, claims are not limited to the manipulations of the recited step(s), but only the structure implied by the steps. MPEP § 2113 states:

> [E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)* (citations omitted).

A product does not have to be made by the same process in order to be the same product, because a product is a product, no matter how it is claimed. Applicants have not shown that the alleged difference(s) in the process results in a product that is structurally different from the product of the prior art. In the instant case, Applicants have not shown the underlying structure of the prior art antigenic polypeptide differs from that of the instantly claimed antigen of the amino acid sequence of SEQ ID NO: 3.

Contrary to Applicants' assertion, there is no indication or disclosure in the '132 patent and the Cover's 1992 reference to demonstrate that the prior art purification scheme resulted in a greater than 5000-fold increase in the toxicity of their 23 amino acid-long polypeptide that shows 100% sequence identity with the instantly claimed polypeptide fragment. Furthermore, with regard to Cover *et al.* (1992), it is important to note Applicants' admission within the instant specification. In the first part of page 6 of the specification, Applicants cite Cover *et al.* (1992) and state that 'the previously described 87 kDa results from either the further processing of the 100 kDa protein or from proteolytic degradation of a larger protein during purification'. See also lines 27-30 on page 47 of the specification. The fourth full paragraph on page 45 of Applicants' specification acknowledges that the amino acid fragment encoded by the nucleotides 116-413 of

the sequence shown in Figure 1 (i.e., SEQ ID NO: 2) and fused to a part of the MS2 polypeptide includes 'the 23 amino acids previously identified'. The specification at lines 10-14 of page 47 readily admits that this 23 amino acid-long sequence is identified as 'the amino terminus of the previously described 87 kDa vacuolating protein, ...J. Biol. Chem. 267: 10570-75 (1992)'.

The Office has met the burden and the art rejections stand.

Double Patenting Rejection(s)

12) Claims 45 and 46 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 40, 54, 61-65, 72-75, 82-86, 93 and 94 of the co-pending application, SN 09/360,934. Although the conflicting claims are not identical, they are not patentably distinct from each other because the product(s) claimed in the cited claims are encompassed within the scope of the instant claims.

Rejection(s) under 35 U.S.C. § 102

13) Claims 38 and 45 are rejected under 35 U.S.C. § 102(e) as being anticipated by Cover *et al.* (US 6,054,132, filed 02/26/1992 – already of record). See also paragraph 10 above.

The limitation "toxicity" in this rejection is interpreted as encompassing toxicity due to endotoxin. It is also noted that the limitation "toxicity" encompasses general toxicity. It is further noted that the transitional recitation "comprising" is open-ended claim language and therefore does not exclude additional, unrecited elements. See MPEP 2111.03 [R-1].

Cover *et al.* ('132) disclosed antigenic fragments of a cell vacuolating toxin (i.e., cytotoxin) of *Helicobacter pylori* which is recombinantly or synthetically produced and a composition comprising the same (see column 2, lines 25-58). A 23 amino acid-long N terminal fragment of the toxin antigen, i.e., SEQ ID NO: 1, AFFTTVIIPAIVGGIATGTAVGT, obtained from the purified toxin is taught (see column 10, lines 2--4; and first sequence in columns 17 and 18 under Sequence Listing). This 23 amino acid-long antigenic fragment of the prior art has 100% sequence identity with a 23 amino acid-long contiguous fragment that stretches between positions 34-56 of the instantly recited SEQ ID NO: 3. The antigenic fragment is present along with water, phosphate buffered saline or an adjuvant (see column 18, third paragraph; column 17, second paragraph; and column 16, lines 45-50). That the 23 amino acid-long fragment of the prior art obtained from a purified toxin is pure enough to be of substantially no endotoxicity or exhibits substantially reduced contribution to LPS-related toxicity, and that it is long enough to be immunologically identifiable by an *H. pylori*-specific antibody are inherent from the teachings of Cover *et al.* Given that all the structural elements of the instant claims are met by the prior art antigenic fragment, the immunological identifiability by an antibody specifically reactive with *H. pylori* cytotoxin and the exhibition of substantially no toxicity or of substantially reduced contribution to toxicity, are viewed as the inherent

properties inseparable from the antigenic fragment taught by Cover *et al.* ('132).

Claims 38 and 45 are anticipated by Cover *et al.* ('132).

14) Claims 38 and 45 are rejected under 35 U.S.C. § 102(b) as being anticipated by Cover *et al.* (*J. Biol. Chem.* 267: 10570-10575, 25 May 1992 – already of record) (Cover *et al.*, 1992). See also paragraph 10 above.

The limitation "toxicity" in this rejection is interpreted as encompassing toxicity due to endotoxin. It is also noted that the limitation "toxicity" encompasses general toxicity. It is further noted that the transitional recitation "comprising" is open-ended claim language and therefore does not exclude additional, unrecited elements. See MPEP 2111.03 [R-1].

Cover *et al.* (1992) disclosed an antigenic N-terminal fragment of a cell vacuolating toxin (i.e., cytotoxin) of *Helicobacter pylori* which is recombinantly or synthetically produced and a composition comprising the same in distilled water (see Table III and page 10571, left column). This 23 amino acid-long fragment obtained from the purified toxin antigen, AFFTTVIIPAIVGGIATGTAVGT, has 100% sequence identity with a 23 amino acid-long contiguous fragment that stretches between positions 34-56 of the instantly recited SEQ ID NO: 3. That the 23 amino acid-long fragment of the prior art obtained from a purified toxin is pure enough to be of substantially no endotoxicity or exhibits substantially reduced contribution to LPS-related toxicity, and that it is long enough to be immunologically identifiable by an *H. pylori*-specific antibody are inherent from the teachings of Cover *et al.* (1992). Given that all the structural elements of the instant claims are met by the prior art antigenic fragment, the immunological identifiability by an antibody specifically reactive with *H. pylori* cytotoxin and the exhibition of substantially no toxicity or of substantially reduced contribution to toxicity, are viewed as the inherent or intrinsic properties inseparable from the antigenic fragment taught by Cover *et al.* (1992).

Furthermore, the term "recombinantly produced" in the claim represents a process limitation. When claims are drawn to a product-by-process, claims are not limited to the manipulations of the recited step(s), but only the structure implied by the steps. MPEP § 2113 states:

> [E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)* (citations omitted).

A product does not have to be made by the same process in order to be the same product, because a product is a product, no matter how it is claimed. Applicants have not shown that the alleged difference(s) in the process results in a product that is structurally different from the product of the prior art. In the instant case,

Applicants have not shown the underlying structure of the prior art antigenic polypeptide fragment differs from that of the instantly claimed fragment of the amino acid sequence of SEQ ID NO: 3.

Claims 38 and 45 are anticipated by Cover *et al.* (1992).

Remarks

15) Claims 38 and 44-46 stand rejected.

16) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

17) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

March, 2004

S. DEVI, PH.D.
PRIMARY EXAMINER